U.S. Measurement System

NIST National Institute of Standards and Technology

Imaging as a Biomarker: Standards for Change Measurements in Therapy

Breakout Area 2: PET & PET CT:
What can be measured over time?

Day 2: Summary
"The Detailed Measurement Science & Standards Needs – The What by When and by Whom"
Near, Mid-Term Issues Only

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Breakout Area 2: PET & PET/CT:
What can be measured over time?
Measurement Need #1 for Near-Term 1-3 Years

1. *Technology at Issue:* Imaging response to lung cancer therapy with FDG
2. *Submitter(s):* Participants of Breakout Area 2.
3. *Technological Innovation at Stake:* There is recognized potential for the use PET/CT imaging with FDG to asses response to therapy. For trials of new therapies, however, multi-center trials are needed for accrual and statistical power. With widespread availability of FDG PET/CT, imaging biomarker results need to be compatible across sites.
4. *Economic Significance of Innovation*: Faster and less expensive trials by improving statistical power. PET images can actually be the key factor in approval for new therapies. Consequent delivery on new medications for unmet medical needs. Fewer failures for individual patients. Trickle-down of improved imaging protocols to clinical practice.
5. *Technical Barriers to the Innovation*: (1) Significant variability in estimating tracer uptake due to differences in scanner algorithms, processing parameters, partial volume effects, and across-tumor heterogeneity. Problems are increased for older scanners. (2) The often unknown longitudinal stability of scanners. (3) Operator errors in protocol compliance, calibration, acquisition, process of measurement, and/or analysis. Integration of trial protocol into on-site clinical practice.
6. *Stage of Innovation Where Barrier Appears*: The use of PET/CT imaging.

Breakout Area 2: PET & PET/CT : What can be measured over time? Measurement Need #1 for Near-Term 1-3 Years (cont'd)

7. *Measurement-Problem Part of Technical Barrier*: The variability in estimating tracer uptake due to differences in scanner algorithms, processing parameters, partial volume effects, and method of reporting (e.g. max vs. mean SUV or other metrics, as well as ROI definition for smaller lesions). Specifically across platforms and or sites. Accurate times for all aspects. Calibrations. Variations in DICOM interpretation/implementation. Insufficient header fields in DICOM headers for needed image information for clinical trials
8. *Potential Solutions to Measurement Problem:* (1) Standardized phantom relevant to imaging task with different lesion sizes. At a minimum this would be imaged on representative scanners (i.e. one from each Mfgr.) or potentially imaged as a qualification step by every participating imaging site. Potentially combined with CT DQC phantom (2) Introduction of QA trending tools to plot QA results as a routine procedure. (3) Digital phantom images to test Mfrs. display and analysis tools, in particular SUV values and ROI definitions and estimated values. (4) Incorporating information needed into daily QA/QC. (5) Operator manual and/or training.(6) Use of FBP for images used to report quantitative results, in addition to iterative methods if used. (7) NIST timing standards time, weight activity.(8) Standards for site qualification
9. *Potential Providers of Solutions:* Standards for site qualification: ICANNL, SNM, ACR, AAPM Standards organizations: AAPM, NEMA Specific design for phantoms and QC:SNM, ACRIN, AAPM NIST NEMA. Implementation/users: Scanner Mfgs, Pharma, CROs, Oncology cooperative groups (SWOG, CALGB, ASCO, ASTRO,...)
10. *What is the role for Government, if Any?:* Scientific and programmatic support by NIH and NIST. NIST assistance with phantom definition and longitudinal scanner calibration and timing standards time, weight and activity. NIST assistance with standards definitions.
11. *If There is a Government Role, Why Industry Says It Can't/Won't Pay for That Part of Solution:* No financial incentive (yet).

Breakout Area 2: PET & PET/CT: What can be measured over time?

Measurement Need #2 for Near-Term 1-3 Years

1. *Technology at Issue:* Imaging progression of Alzheimer's in ADNI study
2. *Submitter(s):* Participants of Breakout Area 2
3. *Technological Innovation at Stake:* Acquisition of FDG PET/CT brain images will provide a large database for hypothesis testing in clinical neuroimaging.
4. *Economic Significance of Innovation*: Help to design imaging trials with fewer patients and increased ability to detect smaller changes.
5. *Technical Barrier to the Innovation*: Patient motion between emission and transmission/CT scan, leading to potentially confounding errors in FDG uptake. Small size of changes looked for. Variability in normal patients. In addition most of the barriers (and solutions) raised in the previous document *Imaging response to lung cancer therapy with FDG* apply.
6. *Stage of Innovation Where Barrier Appears*: Acquisition of images for ADNI study

Breakout Area 2: PET & PET/CT: What can be measured over time?

Measurement Need #2 for Near-Term 1-3 Years (cont'd)

7. *Measurement-Problem Part of Technical Barrier*: Small head motions between emission and transmission/CT scan lead to inaccuracies is attenuation correction. These resulting effects in the tracer uptake image are small, but Alzheimer's studies can rely on changes of only a few percent per year. Amount of motion and consequent impact on PET brain image is unknown on a patient-by-patient case. (2) Normal variability
8. *Potential Solutions to Measurement Problem:* (0) A good head-holder (1) Automated estimation of motion (i.e. rigid-body image registration using mutual information cost functions), followed by re-alignment of emission and transmission/CT scan data before attenuation correction. (2) Head motion tracking with position-sensing devices (e.g. Polaris, Varian RPM), also followed by re-alignment of emission and transmission/CT scan data before attenuation correction. (3) Use of open source normals database to determine statistical significance.
9. *Potential Providers of Solutions:* For (0-1): Third-party vendors, Scanner Mfrs,. For (2) and Academia. For (3) ADNI and neuoimaging societies
10. *What is the role for Government, if Any?:* Scientific and programmatic support by NIH.
11. *If There is a Government Role, Why Industry Says It Can't/Won't Pay for That Part of Solution:* Industry hasn't been asked until today, small market so far.

Breakout Area 2: PET & PET/CT
What can be measured over time?
Measurement Need #1 for Mid-Term and Long Term 3-5 Years

1. *Technology at Issue:* Development of specific molecular probes, e.g. hypoxia markers, nucleoside transporters, and steroid receptor assays.
2. *Submitter(s):* Participants of Breakout Area 2
3. *Technological Innovation at Stake:* Development of specific molecular probes predictive assay of treatment response. Treatment stratification, proteomic profiling of disease. Individualized therapy.
4. *Economic Significance of Innovation*: Providing data for CMS assessment of appropriateness criteria. Faster and less expensive trials of new therapies by improving statistical power. Consequent delivery on new medications for unmet medical needs. Fewer failures for individual patients. Trickle-down of improved imaging protocols to clinical practice. Individualized therapy. Expansion of the use of PET/CT with new tracers.
5. *Technical Barrier to the Innovation*: "Cottage Industry" in academic, industry, and pharma, leading to uncoordinated efforts (only counter-example is NCI sponsored FLT trial), also leads to IP-driven lack of information sharing.. Several different (i.e. competing) tracers under evaluation (e.g hypoxia and neuroedocrine tumor markers). How do we analyze the studies? (i.e. ranging from full kinetic models with arterial sampling to 'simple' SUV). Regulatory burden. Clinical trial design. Correlation of outcomes.
6. *Stage of Innovation Where Barrier Appears*: All stages from proof-of-concept through phase III trials. Cost w.r.t. market size.

Breakout Area 2: PET & PET/CT
What can be measured over time?
Measurement Need #1 for Mid-Term 3-5 Years (cont'd)

7. *Measurement-Problem Part of Technical Barrier*: How do we analyze the studies? (i.e. ranging from full kinetic models with arterial sampling to 'simple' SUV). Also basic issues of the variability in estimating tracer uptake due to differences in scanner algorithms, processing parameters, partial volume effects, and method of reporting (e.g. max vs. mean SUV or other metrics, as well as ROI definition for smaller lesions).
8. *Potential Solutions to Measurement Problem:* Standardized phantom relevant to imaging task. Standardized analysis and reporting methods. Presence of a independent facilitator for standards. Acceleration of introduction of new probes in conjunction with larger clinical trials.
9. *Potential Providers of Solutions:* FDA, Pharma, Oncology cooperative groups. Medical imaging societies (SNM, RSNA, ACR, ACRIN). NIH
10. *What is the role for Government, if Any?:* Scientific and programmatic support by NIH. FDA is needed for approval of new tracers. NIST could provide the independent facilitator for standards.
11. *If There is a Government Role, Why Industry Says It Can't/Won't Pay for That Part of Solution:* No short-term financial benefit.

Topics in using PET/CT for assessing change that should have been covered

- Time of Flight PET - impact of new technology over next 1-5 years
- SPECT - many more tracers, but non-quantitative
- SPECT/CT - new technology, not widely distributed
- Cardiac Imaging:
  - Difficulties introduced by PET/CT with CT-based attenuation correction
  - Integration of PET and CT angiography
- New tracers/Drug discovery
- Respiratory motion
- Pre-clinical validation
- Image data for IGRT, IMRT and RIT
- Tumor heterogeneity